References and Notes

(1) (a) Reported in preliminary form: J. W. Lown and M. H. Akhtar, *J. Chem. Soc., Chem. Commun.*, 829 (1972). (b) We are indebted to the National Research Council of Canada (Grant A2305) for financial aid. (c) National Research Council of Canada Postdoctoral Fellow.
(2) R. Breslow, *Accounts Chem. Res.*, **6**, 393 (1973); R. Breslow, J. Brown, and J. J. Gajewski, *J. Amer. Chem. Soc.*, **89**, 4383 (1967); R. Breslow, *Angew. Chem., Int. Ed. Engl.*, **7**, 565 (1968).
(3) S. Winstein in "Aromaticity," Special Publication No. 21, The Chemical Society, London, 1967, pp 5–45.
(4) H. Beinert, "The Enzymes," Vol. II, P. D. Boyer, H. Lardy and K. Myrback, Ed., Academic Press, New York, N. Y., 1960, Chapter 10.
(5) D. W. Woolley, *J. Biol. Chem.*, **154**, 31 (1944).
(6) (a) O. Shimomura and F. H. Johnson, *Tetrahedron Lett.*, 2963 (1973); (b) K. Hori, J. E. Wampler, and M. J. Cormier, *J. Chem. Soc., Chem. Commun.*, 492 (1973); (c) F. McCapra and M. J. Manning, *ibid.*, 467 (1973); (d) T. Goto, M. Isobe, D. A. Coviello, Y. Kishi, and S. Inoue, *Tetrahedron*, **29**, 2035 (1973).
(7) A. T. Mason and G. R. Winder, *J. Chem. Soc.*, **63**, 1355 (1893).
(8) S.-J. Chen and F. W. Fowler, *J. Org. Chem.*, **35**, 3987 (1970).
(9) S.-J. Chen and F. W. Fowler, *J. Org. Chem.*, **36**, 4025 (1971).
(10) This rapid oxidation of **1** by air parallels the similar behavior of the structurally related 5,10-dihydrophenazines [H. McIlwain, *J. Chem. Soc.*, 1704 (1937)] and phenoxazine (D. E. Pearson in "Heterocyclic Compounds," Vol. 6, Wiley, New York, N. Y., 1957, Chapter 14).
(11) P. B. Ayscough in "Electron Spin Resonance in Chemistry," Methuen, London, 1967, p 15.
(12) (a) J. R. Bolton, A. Carrington, and J. dos Santos-Veiga, *Mol. Phys.*, **5**, 465 (1963); (b) B. L. Barton and G. K. Fraenkel, *J. Chem. Phys.*, **41**, 1455 (1964).
(13) A. Castellano, J. P. Catteau, and A. Lablanche-Combier, *J. Chem. Soc., Chem. Commun.*, 1207 (1972).
(14) (a) V. I. Denes and G. Ciurdaru, *Chem. Commun.*, 510 (1970); (b) Y. Ueno, T. Nakai, and M. Okawara, *Bull. Chem. Soc. Jap.*, **43**, 162, 168 (1970); (c) Y. Araki, *ibid.*, **43**, 252 (1970).
(15) (a) D. Bormann, *Chem. Ber.*, **103**, 1797 (1970); (b) R. R. Engel and D. Liotta, *J. Chem. Soc. C*, 523 (1970).
(16) In a recent review of 1,3-alkyl migrations, Landis states, "The mechanistic paths of most 1,3-rearrangements are still merely conjecture:" P. S. Landis, "Mechanisms of Molecular Migrations," Vol. 2, B. S. Thyagarajan, Ed., Wiley, New York, N. Y., 1969, Chapter 2.
(17) In comparable experiments by Wiberg and cowrokers ^{13}C-enriched alkyl styryl ethers rearranged to the corresponding propiophenones with virtually complete scrambling of the groups: K. B. Wiberg, T. M. Shryne, and R. R. Kintner, *J. Amer. Chem. Soc.*, **79**, 3160 (1957).
(18) T. G. Traylor, quoted by E. M. Kosower in "An Introduction to Physical Organic Chemistry," Wiley, New York, N. Y., 1968 p 357.
(19) K. Biemann, "Mass Spectromety—Organic Chemical Applications," McGraw-Hill, New York, N. Y., 1962, p 59.
(20) This type of addition is not unexpected, since it has already been demonstrated that alcohols add reversibly to compounds similar to **1a** in this manner: J. W. Lown and M. H. Akhtar, *J. Chem. Soc., Perkin Trans. 1*, 683 (1973).
(21) (a) H. Iwamura, M. Iwamura, T. Nishida, and I. Miura, *Tetrahedron Lett.*, 3117 (1970); (b) H. Iwamura, M. Iwamura, T. Nishida, and S. Sato, *J. Amer. Chem. Soc.*, **92**, 7474 (1970).
(22) J. Jacobus, *Chem. Commun.*, 709 (1970).
(23) N. A. Porter, L. M. Marnett, C. H. Lochmuller, G. L. Closs, and M. Shobataki, *J. Amer. Chem. Soc.*, **94**, 3664 (1972).
(24) Difficulties encountered in measuring rates owing to sensitivity of the solutions to light and oxygen and of the narrow temperature range available render these values only very approximate.
(25) U. Eisner and J. Kuthan, *Chem. Rev.*, **72**, 1 (1972).
(26) (a) T. L. Gilchrist, G. E. Gymer, and C. W. Rees, *Chem. Commun.*, 1519 (1971); (b) D. J. Anderson, T. L. Gilchrist, G. E. Gymer, and C. W. Rees, *ibid.*, 1518 (1971).
(27) W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966, p 157.
(28) Reference 27, p 119.
(29) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970, p 119.
(30) (a) K. R. Kopecky and T. Gillan, *Can. J. Chem.*, **47**, 2371 (1969); (b) F. D. Greene, M. A. Berwick, and J. C. Stowell, *J. Amer. Chem. Soc.*, **92**, 867 (1970).
(31) W. von E. Doering, M. Barber, M. Sprecher, and K. B. Wiberg, *J. Amer. Chem. Soc.*, **74**, 3000 (1952).
(32) A. Streitwieser and J. R. Wolfe, *J. Org. Chem.*, **28**, 3263 (1963); *J. Amer. Chem. Soc.*, **79**, 903 (1957).
(33) H. Gerlach, *Helv. Chim. Acta*, **49**, 2481 (1966).
(34) J. H. Brewster and M. W. Kline, *J. Amer. Chem. Soc.*, **74**, 5179 (1952).
(35) The base-catalyzed Stevens rearrangement has recently been demonstrated to proceed by a radical dissociation–recombination mechanism [U. Schollkopf, U. Ludwig, G. Ostermann, and M. Patsch, *Tetrahedron Lett.*, 3415 (1969)] and is known to proceed with >96% retention for migration of PhCHMe.[34,35] The reasonable assumption is made that a similar retention obtains for migration of PhCHD– so the absolute configuration of (−)-**29** is established.
(36) (a) J. E. Baldwin, W. F. Erickson, R. E. Hackler, and R. M. Scott, *Chem. Commun.*, 576 (1970); (b) J. E. Baldwin and W. F. Erickson, *ibid.*, 359 (1971); (c) J. E. Baldwin and C. H. Armstrong, *ibid.*, 631 (1970); (d) J. E. Baldwin, J. E. Brown, and R. W. Cordell, *ibid.*, 31 (1970); (e) J. E. Baldwin, J. E. Brown, and G. Hofle, *J. Amer. Chem. Soc.*, **93**, 788 (1971); (f) J. E. Baldwin and J. E. Patrick, *ibid.*, **93**, 3556 (1971); (g) J. E. Baldwin and R. E. Hackler, *ibid.*, **91**, 3646 (1969).
(37) (a) M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill, New York, N. Y., 1969; (b) J. F. Labarre and F. Crasmer, *Fortschr. Chem. Forsch.*, **24**, 33 (1971).
(38) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, p 275; N. Trinajstic, *J. Mol. Struct.*, **8**, 236 (1971).
(39) J. W. Lown and M. H. Akhtar, *J. Chem. Soc., Perkin Trans. 1*, 683 (1973).
(40) P. Wittig and R. Mayer, *Z. Chem.*, **7**, 306 (1967).
(41) F. W. Fowler, *J. Amer. Chem. Soc.*, **94**, 5926 (1972).
(42) R. K. Hills and N. W. Gilman, *Tetrahedron Lett.*, 1421 (1967); (b) Y. Makisumi, *ibid.*, 6413 (1966).
(43) H. Kohn and R. A. Olofson, *J. Org. Chem.*, **37**, 3504 (1972).

Synthetic and Mechanistic Aspects of the Sodium Hydride Promoted Acylation of Methylated Heteroaromatics[1]

James F. Wolfe,* D. E. Portlock, and Douglas J. Feuerbach

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061

Received February 15, 1974

A series of representative α- and γ-methylated heteroaromatic azines and diazines were acylated with benzoate, trifluoroacetate, nicotinate, oxalate, and phthalate esters using sodium hydride as the condensing agent to afford heteroarylmethyl ketones, ethyl heteroarylpyruvates, and 2-heteroaryl-1,3-indandiones, respectively. Rates of acylation of quinaldine, as determined by hydrogen-evolution measurements, were shown to be independent of alkoxide concentration, but dependent upon both the concentration and polarity of the carbonyl group of the acylating ester. These results are attributed to accelerated ionization of a lateral proton from a complex involving ester and heterocycle.

Acylations of methylated heteroaromatics to afford ketones can be accomplished by initial lateral metalation of the heterocycle with a strong base, followed by treatment of the resulting carbanionic intermediate with an ester.[2] Essentials of the generally accepted mechanism for such reactions are illustrated in Scheme I by the acylation of quinaldine (1) with methyl benzoate.[3] On the basis of extensive studies by Levine and coworkers, alkali amides or alkali salts of certain dialkylamines currently appear to be the most satisfactory reagents for effecting these condensations.[4] Organolithium reagents have found some utility with heterocycles that are not susceptible to nucleophilic addition,[5] while alkoxides have been used in several instances where the acidity of side-chain protons is en-

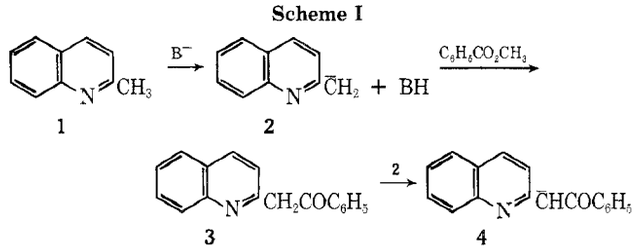
Table I
Acylation of Methylated Heteroaromatics to Form Ketones and α-Keto Esters 6[a]

No.	Product Het	R	Mp or bp, °C (mm)	Yield, %	Rxn time, hr	Recrystn solvent
6a	2-Quinolyl	C_6H_5	119–120[b]	93	18	70% EtOH
6b	2-Quinolyl	p-ClC_6H_4	163–164[c]	72	8	EtOH
6c	4-Quinolyl	C_6H_5	116–117[d]	98	48	i-PrOH
6d	2-Pyridyl	C_6H_5	190–192[e] (7)	92	48	
6e	4-Pyridyl	C_6H_5	115–116[f]	92	48	Benzene
6f	2-Pyrazyl	C_6H_5	80–82[g]	80	8	DMF
6g	2-Quinoxalyl	C_6H_5	152–153[h]	82	2	EtOH
6h	3-Methyl-2-quinoxalyl	C_6H_5	125–126[i,j]	52	7	Hexane
6i	2-Benzoxazolyl	3-Pyridyl	133–135[k]	78	4	i-PrOH
6j	2-Quinoxalyl	CF_3	150–152[l]	79	1	95% EtOH
6k	2-Quinoxalyl	CO_2Et	164–165[m]	72	4	Heptane
6l	3-Methyl-2-quinoxalyl	CO_2Et	126–128[n]	88	4	50% EtOH

[a] Acylating esters were methyl benzoate, methyl p-chlorobenzoate, ethyl nicotinate, ethyl trifluoroacetate, and diethyl oxalate. [b] Lit.[2b] mp 114–116°. [c] *Anal.* Calcd for $C_{17}H_{12}ClNO$: C, 72.47; H, 4.26; N, 4.97. Found: C, 72.52; H, 4.20; N, 4.78. [d] Lit.[2b] mp 115°. [e] Lit.[2b] bp 150–160° (3–4 mm). [f] Lit.[5d] mp 112–113°. [g] Lit.[5c] mp 82–83°. [h] *Anal.* Calcd for $C_{16}H_{12}N_2O$: C, 77.42; H, 4.84; N, 11.29. Found: C, 77.59; H, 4.97; N, 11.19. [i] Lit.[2a] mp 125.6–126.5°. [j] Diphenacyl derivative **7a** (32%) was isolated from this reaction, mp 205–207° (lit.[2a] mp 204.5–205.2°). [k] *Anal.* Calcd for $C_{14}H_{10}N_2O_2$: C, 70.59; H, 4.20; N, 11.76. Found: C, 70.84; H, 4.17; N, 12.04. [l] *Anal.* Calcd for $C_{11}H_7F_3N_2O$: C, 55.0; H, 2.94; N, 11.67. Found: C, 55.21; H, 2.69; N, 11.80. [m] Lit. mp 162°: N. J. Leonard and J. H. Boyer, *J. Amer. Chem. Soc.*, **77**, 2980 (1950). [n] Lit. mp 129°: G. M. Bennet and G. H. Willis, *J. Chem. Soc.*, 1928 (1960).

hanced by N-oxide,[6] nitro,[7] and carboalkoxy[8] functions or a second heteroatom.[9]

Scheme I



However, even with amide bases, these acylations suffer from an inherent disadvantage in that carbanions such as **2** usually abstract a methylene proton from intermediates of type **3**, to form weakly basic carbanions **4**, more rapidly than they react with ester. Thus, when a 1:1:1 molar ratio of heterocycle to base to ester is employed, only one-half of the heteroaromatic and ester are consumed. Attempts to circumvent this problem by using an extra equivalent of base have met with limited success owing to the tendency of many commonly employed bases to react with the acylating agent.[10] Consequently, these condensations are routinely carried out with a 2:2:1 molar ratio of heterocycle to base to ester. Although such procedures increase the efficiency of ester consumption, a molecular equivalent of starting heterocycle remains unchanged, and must be removed from the desired product. Moreover, if the heterocyclic reactant is precious, the disadvantage of such a sequence is obvious.

It seemed to us that the key to overcoming the unfavorable stoichiometry of these acylations, especially those utilizing esters having no α hydrogens, might be found in the use of sodium hydride as the condensing agent. This was based on the fact that sodium hydride is a strong base, but weakly nucleophilic,[11] and might therefore be used in excess without attacking either the ester carbonyl or the nucleus of the heterocyclic substrate. In spite of such potentially favorable properties, sodium hydride has been rarely employed in the acylation of alkylated heteroaromatics,[12] perhaps because of reports that weakly acidic heterocycles such as α- and γ-picoline and quinaldine (**1**) give little or no evidence of salt formation with sodium hydride in DMF,[13] THF,[14] or HMPA.[15]

We now wish to report that sodium hydride is a very effective base for acylations of a variety of methylated heteroaromatics, and that the mechanism of one such reaction is more complex than the series of steps shown in Scheme I.

Results and Discussion

Synthetic Applications. In accord with results of other investigators,[13-15] we observed that less than 0.5 molar equiv of hydrogen was generated upon treatment of quinaldine (**1**) with excess sodium hydride in refluxing 1,2-dimethoxyethane (DME) for 18 hr. However, addition of a mixture of **1** and methyl benzoate (1:1.2 molar ratio) to excess sodium hydride in refluxing DME resulted in evolution of 2 molar equiv of hydrogen in 18 hr, and 2-phenacylquinoline (**6a**) was produced in 93% yield based on **1**. The generality of this procedure was demonstrated by acylations of a representative series of methylated heteroaromatics (**5**) with benzoate, picolinate, trifluoroacetate, and oxalate esters to afford ketones **6a–j** and α-keto esters **6k,l**. Results of these experiments are summarized in

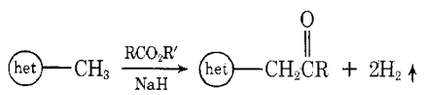


Table I, where it may be seen that yields of acylated products were quite satisfactory. Reaction times necessary for complete hydrogen evolution varied with acidity of the heterocyclic substrate and nature of the acylating ester. For example, reaction of methyl benzoate with 2-methylquinoxaline to give **6g** was essentially complete after 2 hr, while acylation of α-picoline with the same ester to give **6d** required 48 hr for complete hydrogen evolution. Reaction of **1** with methyl p-chlorobenzoate to afford **6b** proceeded significantly faster than the analogous acylation of **1** with methyl benzoate.

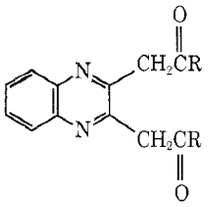
Twofold acylations of 2,3-dimethylquinoxaline with excess methyl benzoate and diethyl oxalate gave **7a** and **7b**, respectively. However, 2,6-lutidine underwent mainly monobenzoylation to afford **8** (39%) accompanied by only

Table II
Acylation of Methylated Heteroaromatics with Diethyl Phthalate

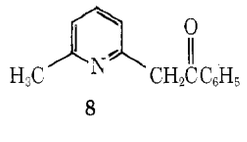
Product					
No.	Het	Mp, °C	Yield, %	Rxn time, hr	Recrystn solvent
10a	2-Pyridyl	295–296[a]	44	60	95% EtOH
10b	4-Pyridyl	323–324[b]	72	80	95% EtOH
10c	2-Quinolyl	242–243[c]	78	18	Benzene
10d	4-Quinolyl	318–319[d]	82	24	95% EtOH
10e	2-Pyrazyl	313–314[e]	93	15	MeOH
10f	2-Quinoxalyl	309–310[f]	65	7	HOAc
10g	3-Methyl-2-quinoxalyl	224–225[g]	64	7	EtOH
10h	2-Benzothiazolyl	363–364[h]	78	2	DMF

[a] Lit.[16b] mp 292°. [b] Lit.[16b] mp 325°. [c] Lit.[15] mp 238–239°. [d] *Anal.* Calcd for $C_{15}H_{11}NO_2$: C, 79.12; H, 4.03; N, 5.13. Found: C, 79.40; H, 4.03; N, 5.11. [e] Lit.[17] mp 309–310°. [f] *Anal.* Calcd for $C_{17}H_{10}N_2O_2$: C, 74.45; H, 3.65; N, 10.22. Found: C, 74.62; H, 3.72; N, 10.35. [g] *Anal.* Calcd for $C_{18}H_{12}N_2O_2$: C, 75.0; H, 4.17; N, 9.72. Found: C, 74.76; H, 4.05; N, 9.90. [h] Lit. mp >320°: P. Jacobson, *Ber.*, **21**, 2630 (1888).

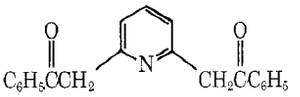
6% of diphenacyl derivative **9** upon prolonged treatment with excess methyl benzoate.



7a, R = C_6H_5
b, R = CO_2Et

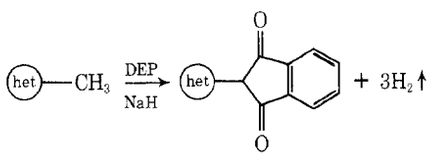


8



9

Reaction of diethyl phthalate (DEP) with a series of methylated heteroaromatics afforded 2-heteroaryl-1,3-indandiones **10** in good yields (Table II). Previous synthet-



10

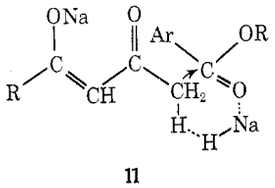
ic methods leading to compounds **10** have involved condensations of heteroaryl aldehydes with phthalides,[16] reaction of heteroarylacetic acids with phthalic anhydride,[17] and treatment of 1,3-indandiones with azine *N*-oxides in the presence of acetic anhydride.[18] In instances where comparisons can be made, the present yields are comparable to or better than those obtained in such syntheses. The sodium hydride method is also attractive because of the ready availability of starting materials.

Several limitations discovered in the present synthetic endeavors are worthy of note. For example, β-picoline failed to undergo appreciable acylation with either methyl benzoate or DEP. Thus, it would appear that methyl groups β to an azomethine function will be acylated with difficulty by this method, whereas reactions at α- and γ-methyl groups occur readily (Tables I and II). Attempted reaction of α-picoline with *n*-propyl nitrate failed to yield any of the expected oxime.[12b] 2-Methylbenzimidazole was recovered unchanged following treatment with methyl benzoate and excess sodium hydride. In this case, initial ionization of the nuclear NH proton apparently reduces the acidity of the methyl protons to the point where sodium hydride cannot effect their removal.

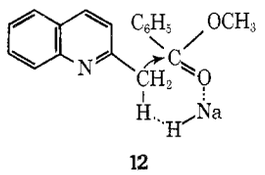
Mechanistic Studies. As pointed out in the previous section, the rate of hydrogen evolution observed upon treatment of **1** with sodium hydride in DME increased rapidly when methyl benzoate was present in the reaction mixture. Of ocurse, this would be expected to some degree since reaction of carbanion **2** with ester should form ketone **3**, which would then lose a methylene proton to generate carbanion **4** and release an equivalent amount of hydrogen. If formation of **2** were the rate-determining step, as it appeared to be on the basis of results with sodium hydride alone, then the rate of hydrogen evolution in the presence of ester should never be greater than twice that observed in its absence. This twofold maximum should likewise not be exceeded in the presence of excess ester. Comparisons of the rates of hydrogen release obtained by treating **1** with sodium hydride alone, with sodium hydride and 1.2 equiv of methyl benzoate, and with sodium hydride and 2.4 equiv of methyl benzoate clearly demonstrated that the rates of hydrogen production in the presence of ester exceeded the expected twofold increase. Moreover, the rate of hydrogen evolution was obviously related to ester concentration (Figure 1).

It has been shown that certain Claisen-type condensations employing sodium hydride proceed best in the presence of a catalytic amount of alcohol. In these instances alkoxide is probably the ionizing base, and sodium hydride serves mainly to force the reaction to completion.[19] It seemed possible that methoxide ion, which could be generated either by reaction of methyl benzoate with carbanion **2** or reaction of sodium hydride with traces of methanol present in the ester, might be responsible for the increased rate of hydrogen evolution observed with **1** and methyl benzoate. Comparison of the rates of hydrogen evolution obtained upon treatment of **1** with sodium hydride alone, and with sodium hydride in the presence of either 10 or 100 mol % of sodium methoxide, revealed that methoxide *did not* increase the rate of hydrogen production. Therefore, the rapid hydrogen release in the presence of methyl benzoate cannot be caused by alkoxide.

In an attempt to explain why only 1 equiv of hydrogen was evolved when certain diketones were treated with excess sodium hydride, while an additional 2 equiv was produced upon addition of an aromatic ester. Hauser and coworkers[20] postulated an intermediate such as **11**. It was



11



12

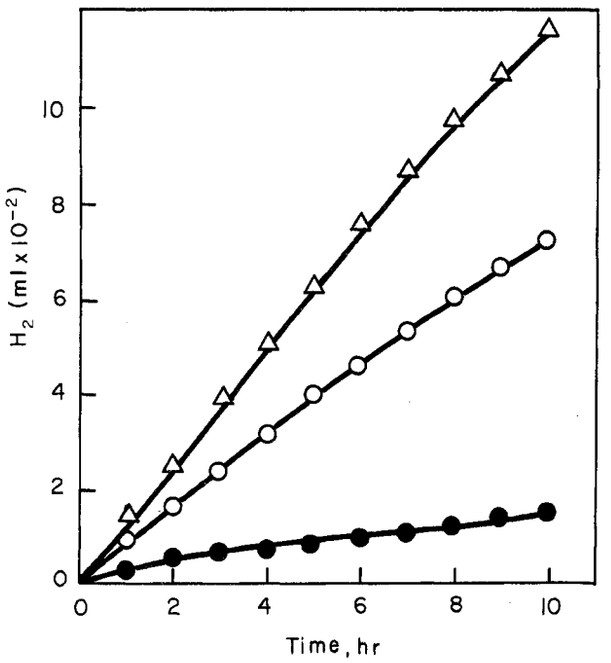


Figure 1. Effect of methyl benzoate concentration on the rate of hydrogen evolution from 1 (0.025 mol) in the presence of excess sodium hydride: ●, without methyl benzoate; ○, with 0.03 mol of methyl benzoate; △, with 0.06 mol of methyl benzoate.

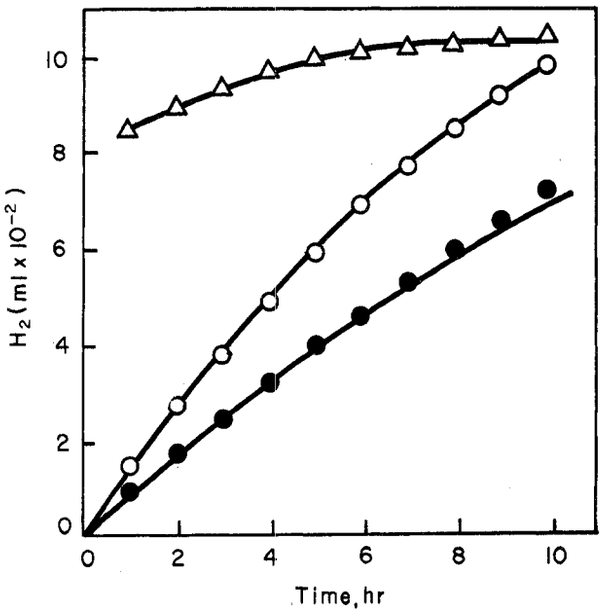
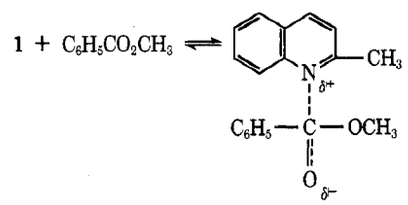


Figure 2. Effect of acylating ester on the rate of hydrogen evolution from 1 (0.025 mol) in the presence of excess sodium hydride: ●, of methyl benzoate (0.03 mol); ○, methyl *p*-chlorobenzoate (0.03 mol); △, ethyl trifluoroacetate (0.03 mol).

proposed that coordination of sodium with ester carbonyl might increase the basicity of hydride ion, thereby facilitating abstraction of a methyl proton to form a terminal carbanion in close proximity to the electrophilic site of the ester. A similar species, **12**, could be imagined for 1, sodium hydride, and methyl benzoate. If such complexation were important it appeared that the role of metal as a mechanistic component might be probed by using lithium hydride. Although lithium hydride is a weaker base than sodium hydride, the greater tendency for coordination expected of lithium might compensate for differences in basicity.[21] Comparable reaction rates for these two bases would then provide strong evidence for the existance of such a coordinative mechanism. However, acylation of 1 with methyl benzoate and lithium hydride proceeded so much slower than the sodium hydride reaction that only 24% of the theoretical amount of hydrogen was evolved after 50 hr.

Although the results with lithium hydride do not definitely rule out a mechanism involving metal complex **12**, we feel that a more attractive explanation of the role of ester might involve interaction between ester and heterocycle in a preionization event. It is suggested then that a complex such as **13** is formed prior to ionization and that



13

the resulting electron deficiency at ring nitrogen facilitates ionization of a methyl hydrogen in a manner similar to that observed upon quaternization of 1.[22] Complexes related to **13** have been proposed to account for changes in

JOC-29-1

EXPERIMENTAL SECTION

General. -- Melting points were taken with a Mel-Temp apparatus and are corrected; boiling points are uncorrected. Infrared spectra were taken on Beckman IR-5A and IR-20A-X spectrophotometers. Pmr spectra were obtained on a Varian Associates A-60 spectrometer with tetramethylsilane as internal standard. Microanalyses were performed in this laboratory by Miss G. D. Tan employing a Perkin Elmer 240 Elemental Analyzer. All reagents were commercial reagent grade. In studies of hydrogen evolution rates, reagents were purified immediately prior to use. 1,2-Dimethoxyethane (DME) was distilled from sodium ribbon and then from sodium hydride. Sodium hydride, as a 50% dispersion in mineral oil, was obtained from Ventron Corporation, Beverly, Mass.

General Procedure for Sodium Hydride Promoted Acylations. -- In a 500 ml three-necked flask equipped with a magnetic stirrer, a pressure-equilizing addition funnel, heating mantle and a reflux condenser, connected at its upper end through a cold trap (Dry Ice-acetone) to a Precision Scientific wet-test meter filled with water, were placed 200 ml of fresh,y distilled DME and 0.25 mol of sodium hydride (prepared by washing 12 g of the commercial dispersion free of mineral oil with petroleum ether). A solution of the appropriate methylated heterocycle (0.05 mol) and ester (0.07 mol) in 100 ml of DME was placed in the addition funnel. The system was flushed with dry nitrogen, then closed to the atmosphere. The solvent in the reaction flask was heated to reflux, and when thermal equilibrium had been established the gas meter was set to zero. The solution of heterocycle and ester was then added over a period of 20 min and the resulting suspension was refluxed until hydrogen evolution ceased. The reaction flask was then cooled in an ice-water bath and 100 ml of ether was added. Next 7.5 g of acetic acid was added dropwise (Caution!), followed by 75 ml of cold water. Finally, an additional 7.5 g of acetic acid and 75 ml of water were added. The resulting two-phase mixture was stirred well and solid products which separated between the layers were collected by suction filtration. The two layers of the filtrate were separated and the aqueous layer extracted with two 150 ml portions of ether. The ethereal extracts and the original organic layer were combined, dried (Na_2SO_4) and concentrated. The last traces of ester and acetic acid were removed at 50-75° (1 mm). The crude product resulting from this operation was added to that which separated between the layers, and the combined material was recrystallized from the appropriate solvent or distilled (Tables I and II).

Twofold acylation of 2,3-dimethylquinoxaline with methyl benzoate was carried out using 7.90 g (0.05 mol) of heterocycle, 21.76 g (0.16 mol) of ester and 12 g of sodium hydride dispersion in 300 ml of DME. The reaction period was 8 hr. Recrystallization of the crude product from absolute ethanol gave 11.45 g (82%) of (7a): mp 206-207.5° (lit.[24] mp 204.5-205.2°); pmr ($CDCl_3$) δ 8.15-7.05 (m, 14H, aromatic) and 2.45 ppm (s, 2H, vinyl H of

JOC-29-2

enol); ir ($CHCl_3$) 6.25 and 6.48 μ (enol).

Similar twofold acylation of 2,3-dimethylquinoxaline with diethyl oxalate was carried out with 0.05 mol of heterocycle, 20.44 g (0.14 mol) of ester, and 12 g of sodium hydride dispersion. After 3 hr the reaction was processed in the usual manner to afford 4.80 g (21%) of 7b as blue-black crystals from absolute ethanol: mp 167-168°; pmr ($CDCl_3$) δ 12.60 (s, 2H, NH or OH), 8.35-7.30 (m, 4H, aromatic), 6.25 (s, 2H, vinyl H of enol), 4.83-5.65 (m, 4H, OCH_2CH_3) and 1.60-0.80 ppm (m, 6H, $-OCH_2CH_3$); ir 5.75 μ (ester C=O) and 6.25 - 6.40 μ (enol).

Anal. Calcd. for $C_{18}H_{18}N_2O_6$: C, 60.34; H, 5.03; N, 7.82. Found: C, 60.60; H, 4.73; N, 7.65.

Attempted dibenzoylation of 2,6-lutidine was conducted using 28.75 g (0.28 mol) of heterocycle, 81.60 g (0.60 mol) of methyl benzoate and 80 g of sodium hydride dispersion in 1000 ml of DME for 120 hr. After the usual work-up the resulting oily, crude product was vacuum distilled. The distillate collected at 194-294° (7mm) solidified on standing and was then recrystallized from hexane to give 20.45 g (39%) of 8: mp 73-76° (lit.[25] mp 77-78°); pmr ($Cl_2CCOCCl_2$) δ 8.05-6.68 (m), 6.26 (s), 5.92 (s) (total 10H) and 2.50 ppm (s, 3H, CH_3); ir ($CHCl_3$) 5.80 (C=O) and 6.02 μ (enol). To the distillation residue was added 120 ml of 95% ethanol and crystals soon formed. They were collected and recrystallized from absolute ethanol to give 4.41 g of diphenacyl derivative 9: mp 92-94° (lit.[27] mp 87°); pmr ($Cl_2CCOCCl_2$) δ 8.05-6.68 (m, 8.26 (s), 5.82 (s) (total 15H), and 4.36 ppm (s, 2H, CH_2); ir ($CHCl_3$) 5.94 (C=O) and 6.12 μ weak (enol).

In addition to the correct analytical data (Tables I and II), new compounds 6b, 8g, 6i, 8i, 10d, 10f and 10g had spectral characteristics consistent with the assigned structures. Ketones of type 6 had a weak ir band at 5.8-5.9 μ accompanied by several strong enol bands at 6.10-6.40 μ. Indandiones 10 exhibited similar absorption at 6.10-6.40 μ but had a much stronger carbonyl band at 5.85-5.95 μ. The pmr ($CDCl_3$) spectra of ketones 6 were characterized by fractional methylene proton resonances at 4.86-4.25 and vinyl proton absorptions at 8.56-8.94 ppm.

Hydrogen Evolution Studies. -- The apparatus described in the previous section was charged with 250 ml of freshly distilled DME and 0.125 mol of washed sodium hydride, and the resulting slurry was brought to reflux. Following attainment of thermal equilibrium, a solution of 1 (0.025 mol) alone or in combination with 0.030 mol of the appropriate ester in 100 ml of DME was added from the addition funnel over a period of 20 min. The cummulative volume of hydrogen evolved was recorded at hourly intervals along with the temperature of the meter and the atmospheric pressure. When hydrogen release stopped, the final meter readings were corrected to standard temperature and pressure and for the vapor pressure of water. In the series of experiments represented in Figure 1, the temperature of the gas

JOC-29-3

meter varied from 21.8 to 22.8° and the atmospheric pressure varied from 700.6 to 711.8 mm. Under these conditions the theoretical volume of 2 equiv of hydrogen is between 1328 and 1339 ml, while that for 1 equiv of hydrogen is between 664 and 669 ml. In the experiments for which data is given in Figure 2, the temperature varied from 23.3 to 27.8° and the pressure varied over the range of 727.7 to 712 mm. The theoretical volume for 2 equiv of hydrogen under these conditions is between 1333 and 1371 ml. Reactions were processed in the usual fashion and products or starting matrials were isolated. Acylation of 1 with ethyl trifluoroacetate gave 6 (R=CF_3): mp 129-130°; pmr ($CDCl_3$) δ 8.07-6.9 (m, 6H) and 5.56 ppm (s, 1H, enol CH).

Anal. Calcd. for $C_{12}H_8NOF_3$: C, 60.25; H, 3.38; N, 5.86. Found: C, 60.40; H, 3.29; N, 6.12.

Hydrogen evolution experiments involving the possible effects of methoxide on the sodium hydride promoted ionization of 1 were conducted on the same scale as described above. The appropriate molar quantities of methoxide were prepared in situ by adding methanol to the sodium hydride-DME slurry prior to attainment of thermal equilibrium and addition of 1.

Attempted benzoylation of 1 using lithium hydride was conducted with molar quantities of reactants identical to those given above.

(26) N. N. Goldberg and R. Levine, J. Amer. Chem. Soc., 77, 4926 (1955).

(27) O. S. Scheuing and L. Winterhalter, Ger. Patent 592849 (1934); Chem. Abstr. 28, 4542 (1934).

the pmr spectra of amides upon addition of pyridine,[23] shifts in the electronic spectrum of pyridazine in the presence of benzophenone,[24] and the rapid rate of which β-keto alcohols effect displacement of halide from 2-halopyridines.[25] As a test of this mechanism we examined the rates of hydrogen evolution accompanying acylations of **1** with methyl *p*-chlorobenzoate and ethyl trifluoroacetate, anticipating that the more positive carbonyl groups of these two esters would favor complex formation. If this occurred, the rates of hydrogen release should exceed the rate observed with methyl benzoate. The indeed proved to be the case, as shown in Figure 2, where it may be seen that the reaction with trifluoroacetate was greater than 60% complete after only 1 hr. It should also be noted that excess methyl benzoate should favor formation of complex **13**, thereby increasing the rate of hydrogen evolution as is observed. Thus, the course of the sodium hydride promoted benzoylation of **1** *via* complex **13** appears to be consistent with our experimental findings. It is also possible that acylations of β-diketone monoenolates in the presence of excess sodium hydride might also involve similar complex formation prior to removal of a terminal methyl proton, since the rates of such reactions are dependent on ester concentration.[20]

Registry No.—**1**, 91-63-4; **6a**, 1531-38-0; **6b**, 51425-11-7; **6c**, 7543-20-6; **6d**, 1620-53-7; **6e**, 1620-55-9; **6f**, 40061-45-8; **6g**, 16310-38-6; **6h**, 51425-12-8; **6i**, 51425-13-9; **6j**, 51425-14-0; **6k**, 7248-83-1; **6l**, 13119-79-4; **7a**, 51425-15-1; **7b**, 51425-16-2; **8**, 1083-25-6; **9**, 51425-17-3; **10d**, 51425-18-4; **10f**, 51425-19-5; **10g**, 51425-20-8; 4-methylquinoline, 491-35-0; 2-methylpyridine, 109-06-8; 4-methylpyridine, 108-89-4; 2-methylpyrazine, 109-08-0; 2-methylquinoxaline, 7251-61-8; 2,3-dimethylquinoxaline, 2379-55-7; methyl benzoate, 93-58-3; methyl *p*-chlorobenzoate, 1126-46-1; ethyl nicotinate, 614-18-6; ethyl trifluoroacetate, 383-63-1; diethyl oxalate, 95-92-1; diethyl phthalate, 84-66-2; 2,6-lutidine, 108-48-5; 2-methylbenzoxazole, 95-21-6.

Miniprint Material Available. Full-sized photocopies of the miniprinted material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the miniprinted and supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2006.

References and Notes

(1) (a) Taken in part from the Ph.D. dissertation of D. E. P., Virginia Polytechnic Institute and State University, 1972. (b) Supported by Public Health Service Research Grants GM 14340 and NS-10197.
(2) For examples, see (a) F. W. Bergstrom and A. Moffat, *J. Amer. Chem. Soc.*, **59**, 1494 (1937); (b) M. J. Weiss and C. R. Hauser, *ibid.*, **71**, 2023 (1949); (c) G. P. Rizzi, *J. Org. Chem.*, **33**, 1333 (1968); (d) R. G. Micetich, *Can. J. Chem.*, **48**, 2006 (1970).
(3) A detailed investigation of this mechanism has been conducted by C. Osuch and R. Levine, *J. Org. Chem.*, **22**, 939 (1957).
(4) See B. M. Baum and R. Levine, *J. Heterocycl. Chem.*, **3**, 272 (1966), and references cited therein.
(5) (a) N. N. Goldberg, L. B. Barkley, and R. Levine, *J. Amer. Chem. Soc.*, **73**, 4301 (1951); (b) A. D. Miller, C. Osuch, N. N. Goldberg, and R. Levine, *ibid.*, **78**, 674 (1956); (c) J. D. Behun and R. Levine, *ibid.*, **81**, 5157 (1959); (d) C. Osuch and R. Levine, *J. Org. Chem.*, **22**, 939 (1957); (e) S. Raynolds and R. Levine, *J. Amer. Chem. Soc.*, **82**, 472 (1960); (f) A. M. Jones, C. A. Russell, and S. Skidmore, *J. Chem. Soc. C*, 2245 (1969).
(6) R. Adams and S. Miyano, *J. Amer. Chem. Soc.*, **76**, 3168 (1954).
(7) B. Frydman, S. Rell, M. E. Despuy, and H. Rapoport, *J. Amer. Chem. Soc.*, **91**, 2338 (1969).
(8) E. Wenkert, P. W. Sprague, and R. L. Webb, *J. Org. Chem.*, **38**, 4305 (1973).
(9) W. Pfleiderer and H. Mosthaf, *Ber.*, **90**, 728 (1957).
(10) (a) M. J. Weiss and C. R. Hauser, *J. Amer. Chem. Soc.*, **71**, 2023 (1949); (b) R. J. Light and C. R. Hauser, *J. Org. Chem.*, **25**, 538 (1960).
(11) Sodium hydride has been shown to be inert toward aromatic esters: F. W. Swamer and C. R. Hauser, *J. Amer. Chem. Soc.*, **68**, 2647 (1946).
(12) (a) For a recent example of the condensation of diethyl carbonate with an activated alkylquinoxaline in the presence of sodium hydride, see D. D. Chapman, *J. Org. Chem.*, **37**, 2498 (1972); (b) Y. Ashani, H. Edery, J. Zahavy, W. Kunberg, and S. Cohen, *Israel J. Chem.*, **3**, 133 (1965), have reported low-yield reactions of 4-methylpyrimidine with nitrite esters in the presence of sodium hydride.
(13) H. E. Zaugg, D. A. Dunnigan, R. J. Michaels, L. R. Swett, T. S. Wang, A. H. Sommers, and R. W. DeNet, *J. Org. Chem.*, **26**, 644 (1961).
(14) H. Normant and T. Cuvigny, *Bull. Soc. Chim. Fr.*, 1881 (1965).
(15) H. Normant, *Angew. Chem., Int. Ed. Engl.*, **6**, 1054 (1967).
(16) (a) S. L. Shapiro, K. Geiger, and L. Freedman, *J. Org. Chem.*, **25**, 1860 (1960); (b) J. G. Lombardino, *ibid.*, **32**, 1988 (1967).
(17) J. G. Lombardino and E. H. Wiseman, *J. Med. Chem.* **11**, 342 (1968).
(18) M. Hamana and M. Yamazaki, *Chem. Pharm. Bull.*, **11**, 411 (1963).
(19) For a discussion of this phenomenon with leading references, see H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 741.
(20) M. L. Miles, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 1007 (1965).
(21) K. M. Mackay, "Hydrogen Compounds of the Metallic Elements," E. & F. N. Spon, Ltd., London, 1966, pp 20–32.
(22) T. I. Abramovitch, I. P. Gragerov, and V. V. Perekalin, *Dokl. Akad. Nauk SSSR*, **121**, 295 (1958).
(23) R. M. Moriority, *J. Org. Chem.* **28**, 1296 (1963).
(24) G. J. Brealey and M. Kasha, *J. Amer. Chem. Soc.*, **77**, 4462 (1955).
(25) R. G. Shepherd and J. L. Fedrick, *Advan. Heterocycl. Chem.*, **4**, 261 (1965).

Chemistry of 2-Tetrahydropyranthiol

Michael G. Missakian,[1] Roger Ketcham,* and Arnold R. Martin

Department of Pharmaceutical Chemistry, University of California, School of Pharmacy, San Francisco, California 94143

Received December 13, 1973

Hydrogen sulfide reacts with 2,3-dihydropyran to form 2-tetrahydropyranthiol (1). 1 has been shown to be a useful reagent for direct introduction of a protected mercaptan into a variety of organic compounds. Addition reactions under ionic and free-radical conditions and displacement reactions have been studied. Subsequent facile cleavage utilizing neutral aqueous silver nitrate followed by treatment of the mercaptide with hydrogen chloride gave the desired mercaptans.

2,3-Dihydropyran reacts with aliphatic and aromatic hydroxyl or sulfhydryl groups under acidic conditions to form alkyl or aryl tetrahydropyranyl ethers[2] or sulfides,[3] respectively. These cyclic acetals and monothioacetals are readily hydrolyzed, in most instances, under mild acid conditions to yield the free alcohol or mercaptan.

It seemed possible that the same protected thiol function might be prepared directly by addition of 2-tetrahydropyranthiol (1) to multiple bonds or by appropriate displacement reactions. Of perhaps greatest interest was the possibility of preparing derivatives of otherwise unstable tautomers such as enethiols or thioimidates. Although our